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## Alterations in Bone Homeostasis and Microstructure Related to Depression and Allostatic Load

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Depression is a severe and highly comorbid condition that affects mental and physical health and is a prime cause of disability. Regarding the pathogenesis of comorbid depressive disorders, previous research has shown that neuroendocrine and neuroanatomical responses to stress lead to cellular and molecular changes that promote the development of comorbid diseases [1]. Hence, depressive disorders may influence the homeostasis of tissues, including bone, and contribute, for example, to osteoporosis development [2, 3] and decreased bone mineral density (BMD) [4]. However, the present knowledge of involved pathogenetic mechanisms is still scarce, and studies are required that provide a better understanding of possible interactions between depression, neuroendocrine stress responses, and bone metabolism. Moreover, it is unclear what comes first: does mental distress, such as depression, impair bone health or does stress-induced disruption of bone homeostasis come first? Both perspectives are highly relevant for the medical care of patients [4], and their study requires the definition of relevant outcomes.

Present stress concepts state that neuroendocrine signaling pathways are activated by stress in an attempt to enable mental as well as physical adaptation and maintain a low allostatic load. However, persistent excessive or prolonged stresses (e.g., traumatic life events, chronic work strain triggering a depressive episode) can provoke a maladaptive increase of neuroendocrine responses, toxic systemic stress, and an accumulation of allostatic load [5]. It is evident that specific allostatic load mediators, such as cortisol, growth hormone, or insulin-like growth factor-I, may play a role in the lifelong remodeling process of bones [6, 7]. Elevated cortisol levels can inhibit osteoblast proliferation, differentiation, and apoptosis, leading to decreased bone density. However, whether such allostatic overload occurs depends largely on exposure intensity and duration, personal and social resources (coping, exposome), and epigenetic adaptability [8]. In other words, stressful life events do not necessarily lead to depressive disorders or allostatic overload, especially if the neuroendocrine response enables adaption and can be turned off after an appropriate interval [9].

Here, we therefore aimed to study whether bone metabolism is changed during an acute depressive episode and whether people with a high life burden and allostatic load show alterations in bone metabolism and mineral density. Further, we wanted to know whether a mathematical algorithm can determine individual allostatic load mediators that identify patients at higher risk for disrupted bone metabolism and thereby optimize medical care.

In an 18-month, multicenter, observational study, we assembled a cohort of two hundred and eight 18- to 65-year-old depressive patients in the primary care setting suffering from severe to moderate depression (mainly ICD-10 F32.x or F33.x). We determined psychosomatic symptoms (Beck Depression Inventory-II [BDI-II]; Symptom Check List – revised [SCL-90-R]: Positive Symptom Distress Index [PSDI], Global Severity Index [GSI], and Positive Symptom Total [PST]), life burden (Inventory of Life Changing Events ), and allostatic load index (ALI; derived from 15 neuroendocrinological, immunological, and metabolic allostatic mediators). Bone metabolism was measured by 3 bone formation and resorption serum markers (osteocalcin [OC], procollagen type 1 N-terminal propeptide [P1NP], and β-CrossLaps [CTx]). BMD was assessed in both hips and the lumbar spine (subsample, $n = 18$; DXA BMD-L1L4, -TMW, -SMW, -GMW, and -HMW). Descriptive statistics, paired sample $t$ tests, multivariable regression models, and Least Absolute Shrinkage and Selection Operator (LASSO) were applied for analyzing the study questions.

65% of our patients (mean age = 46.63, SD = 11.13, f = 75%) suffered from severe to moderate depression (mean BDI-II = 23.61, SD = 10.14), severe psychosomatic symptoms (GSI: 41.8%; PSDI: 42.3%), and allostatic load burden (ALI: 29.3%). Higher life



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**Table 1.** Main effects (regression coefficient b) of depressiveness, life events, psychosomatic symptoms severity, and ALIs on bone markers at baseline ($t_0$)

| | P1NP | | | OC | | | CTx | | |
|---|---|---|---|---|---|---|---|---|---|
| | coefficient | 95% CI | *p* | coefficient | 95% CI | *p* | coefficient | 95% CI | *p* |
| BDI-II sum score | 0.121 | –0.170, 0.413 | 0.417 | **0.083** | –0.008, 0.173 | 0.075 | 0.0004 | –0.002, 0.002 | 0.727 |
| SCL-90-R PSDI | **5.304** | –0.585, 11.194 | 0.081 | **2.631** | 0.855, 4.407 | 0.005 | **0.052** | 0.011, 0.093 | 0.016 |
| SCL-90-R PST | 0.061 | –0.134, 0.256 | 0.543 | 0.045 | –0.015, 0.105 | 0.145 | –0.0002 | –0.002, 0.001 | 0.729 |
| SCL-90-R GSI | 3.222 | –2.103, 8.548 | 0.239 | **2.096** | 0.447, 3.745 | 0.015 | 0.020 | –0.020, 0.059 | 0.333 |
| ILE all[a] | 0.158 | –0.153, 0.470 | 0.317 | **0.111** | 0.017, 0.206 | 0.021 | **0.002** | 0.000, 0.004 | 0.049 |
| ALI 21 | –0.523 | –1.650, 0.604 | 0.365 | **–0.438** | –0.779, –0.096 | 0.014 | **–0.009** | –0.017, –0.001 | 0.025 |
| ALI 15 | –0.435 | –1.759, 0.888 | 0.521 | **–0.462** | –0.864, –0.059 | 0.027 | **–0.009** | –0.018, 0.0005 | 0.065 |
| ALI-II | –0.351 | –1.585, 0.884 | 0.579 | **–0.492** | –0.875, –0.108 | 0.014 | **–0.008** | –0.017, 0.001 | 0.088 |
| ALI-I | 0.734 | –1.824, 3.291 | 0.576 | 0.467 | –0.318, 1.253 | 0.246 | –0.005 | –0.023, 0.014 | 0.614 |

Multiple interaction regression models, adjusted for age, gender, and study sites. Significant regression coefficients are bold ($p < 0.01$, $p < 0.05$, $p < 0.10$; 2-sided testing). ALI, allostatic load index; BDI-II, Beck Depression Inventory II; SCL-90-R, Symptom Check List – revised; PSDI, Positive Symptom Distress Index; PST, Positive Symptom Total; GSI, Global Severity Index; ILE, Inventory of Life Changing Events. [a] Count of all life events.

burden was associated with depressive disorder (BDI-II: b = 0.24 [95% CI 0.064, 0.411], $p = 0.008$) but not with allostatic load.

In this cohort, we observed that higher depression (OC: b = 0.08 [95% CI –0.008, 0.173], $p = 0.075$) and symptom severity (PSDI: P1NP: b = 5.30 [95% CI –0.59, 11.19], $p = 0.081$; OC: b = 0.91 [95% CI 0.86, 4.41], $p = 0.005$; CTX: b = 0.052 [95% CI 0.011, 0.093], $p = 0.016$; GSI: OC: b = 2.10 [95% CI 0.45, 3.75], $p = 0.015$) were associated with a higher expression of anabolic bone metabolism (OC; P1NP; CTx). People with a high life burden showed significantly less anabolic expression (OC: b = 0.11 [95% CI 0.017, 0.206], $p = 0.021$; CTx: b = 0.002 [95% CI 0.000, 0.004], $p = 0.049$).

At the same time, patients with high allostatic load showed a significantly decreased bone metabolism (ALI: OC: b = –0.46 [95% CI –0.864, –0.059], $p = 0.027$; CTx: b = –0.01 [95% CI –0.018, 0.001], $p = 0.065$) and reduced BMD in the lumbar spine and both hips (DXA). LASSO could not identify any singular allostatic load mediator sufficient enough for the prediction of bone metabolism quality (OC; P1NP; CTx) 1.5 years after baseline (Table 1).

The findings suggest that anabolic activation of bone metabolism occurs during a depressive episode, which increases with the severity of the depression and psychosomatic symptoms. This so far undiscovered metabolic adaptation to an exceptionally high stress episode is limited to patients with a higher life burden and completely absent in patients with allostatic overload. The latter are – presumably due to the accumulation of toxic stress in tissues and cells – no longer capable of an adequate metabolic adaptation. Thus, a catabolic and bone damaging process occurs, which is reflected by a reduction of BMD in the long term.

The fact that predominantly patients with acute and nonchronic depressive disorder were involved in the study enabled the discovery of this highly important mechanism that is believed to affect corresponding medical therapies (drug administration, exercise, etc.). The data provide further evidence that a gradation between different levels of physical and mental load accumulation must be respected. However, many questions remain unanswered and should be investigated in further studies. For example, no diagnostic instrument could be derived from the allostatic mediators. In addition, further studies should examine to what extent psychometric data would allow diagnostic assessments [9].

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*Statement of Ethics*

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Final ethical approval was provided on December 11, 2017, from the major institutional ethics review board of the University of Potsdam, Germany (number 15/2017). All participants gave their written informed consent.

*Disclosure Statement*

The authors have no conflicts of interest to declare.

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*Author Contributions*

P.-M.W., K.W.-K.: conceptualization and first draft; P.M.-W., K.W.-K., A.B.: data analysis and interpretation; P.M.-W., A.B., M.R., A.H.: data acquisition. P.M.-W., A.B., I.M.M., E.M.J.P., M.R., A.H., M.A.R., and K.W.-K. substantially improved and revised the manuscript. All authors approved the final version.

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